Genetics of Well-Being

Baselmans, B.M.L.

2018

document version
Publisher's PDF, also known as Version of record

09

A Genetic Investigation of the Well-Being Spectrum

Revise and resubmit as:

Baselmans, B.M.L., van de Weijer, M.P., Abdellaoui, A., Vink, J.M., Hottenga, J.J., Willemsen, G., Nivard, M.G., de Geus, E.J.C., Boomsma, D.I., Bartels, M (2018). A Genetic Investigation of the Well-Being Spectrum

Abstract

The interrelations among well-being, neuroticism and depression can be captured in a so-called well-being spectrum (3-phenotype well-being spectrum, 3-WBS). Several other human traits are likely linked to the 3-WBS. In the present study, we investigate how the 3-WBS can be expanded. First, we constructed polygenic risk scores for the 3-WBS and used this score to predict a series of traits that have been associated with well-being in the literature. We included information on loneliness, big five personality traits, self-rated health, and flourishing. The 3-WBS polygenic score predicted all the original 3-WBS traits and additionally loneliness, self-rated health, and extraversion (R^2 between 1.52-0.69%). Next, using LD score regression, we calculated genetic correlations between the 3-WBS and the traits of interest. From all candidate traits, loneliness and self-rated health were found to have the strongest genetic correlations (r_g= .78, and r_g= .65, respectively) with the 3-WBS. We propose to include these traits in the well-being spectrum and use a 5-phenotype well-being spectrum in future studies to gain more insight into the determinants of human well-being.

Introduction

Many mental disorders share a common genetic liability[1–3]. This common genetic liability offers an explanation as to why many disorders are comorbid or represent highly similar behaviours. While there have been detailed investigations of the genetic similarity and comorbidity of mental disorders, there is much less information about the genetic similarity of mental health traits such as happiness, satisfaction with life, personality, loneliness, self-rated health, and flourishing. Studies on traits that could be considered to be part of a well-being spectrum are important given the large collection of studies pointing to the emotional, cognitive, and interpersonal benefits of high levels of well-being above and beyond the absence of mental disorders[4–6]. Therefore, the aim of this study was to investigate the genetic similarity between several traits associated with well-being, collectively referred to as the "well-being spectrum".

Well-being is a broad and complex construct used to describe optimal psychological functioning[7] and it has been recently proposed to use a spectrum approach[8]. This well-being spectrum (the 3-phenotype well-being spectrum; 3-WBS) captures the phenotypic and genetic overlap between subjective well-being, neuroticism, and depressive symptoms, as has been found in a large genome-wide association study[9]. There are nonetheless other traits that could be considered candidates for inclusion in a broader well-being spectrum. From a phenotypic perspective, it is important to identify such traits in order to get more insight into the aspects influencing human well-being. From a genetic perspective, it is important to identify these traits since their inclusion into the spectrum will help identify more genetic variants that influence human well-being.

One of the associations that has been studied thoroughly is the relationship between well-being and personality. Especially extraversion and conscientiousness have been established as strong positive phenotypic correlates of well-being[10], while neuroticism has been identified as an important negative correlate of well-being[11]. Furhermore, existing literature has established that loneliness, characterized by a sense of emptiness, worthlessness, and a lack of control[12], is negatively associated with well-being[13]. Moreover, self-rated health, a subjective evaluation of one's current health status, has also been pointed out as an important predictor of well-being, due to its high proportion of shared variance with well-being[14,15]. Lastly, while the 3-WBS has included subjective/ hedonic well-being measures (such as satisfaction with life and subjective happiness), it did not yet include psychological or eudaimonic well-being

measures, a well-being domain that involves the fulfilment of human potential [7]. An example of such a measure is flourishing: a person's self-perceived success in several life areas. Previous research on the relationship between psychological/ eudaimonic- and subjective/hedonic well-being have revealed that these two lines of research reflect highly correlated, yet distinguishable constructs[16,17]. Therefore, including both types of well-being could theoretically yield a more integrated conception of the well-being spectrum.

Contrary to the phenotypic associations, few studies have investigated the genetic associations for well-being and associated traits. A genetic investigation of loneliness[18] revealed a strong negative association between a polygenic score for loneliness and subjective well-being, and a positive association with neuroticism and depression, indicating genetic links between the 3-WBS and loneliness. With regard to self-rated health, twin studies have demonstrated that both genes and the environment contribute to the association with well-being[19], but to our knowledge no molecular genetic study is conducted yet. A twin study on the relationship between subjective/hedonic- and psychological/eudaimonic well-being (PWB) indicates a single, genetic factor that accounts for the high heritability in both these constructs[20]. Likewise, a genome-wide association study on hedonic and eudaimonic well-being showed that there is a large overlap in the sets of genes influencing these two traits[17] Lastly, extraversion, and conscientiousness show not only strong phenotypic, but also genetic associations with well-being[21,22].

In this study, we aim to further investigate the well-being spectrum from a genetic perspective. We perform two different types of analyses to compute the genetic associations between the 3-WBS and the likely candidates. We use summary statistics from a large multivariate GWAMA of the 3-WBS[8] to calculate polygenic risk scores to predict satisfaction with life, happiness, neuroticism, depressive symptoms, loneliness, openness to experience, conscientiousness, extraversion, agreeableness, self-rated health, and flourishing.Since the amount of variance explained by polygenic scores can be small even though two traits are highly genetically correlated, we also calculate the standardized proportion of the variance shared by the traits that can be attributed to genetic factors, known as the genetic correlation, using LD score regression.

Materials and Methods

Participants

Participants are voluntary participants in the studies of the Adults Netherlands Twin Register[23,24]. Participants were included if they had filled out questionnaires on one or more of the relevant traits and provided a blood or buccal cell sample for DNA isolation and genotyping. Based on the availability of the data, sample size per analyses varied. An overview of the sample characteristics can be found in Table I and details are provided below.

Subjective Well-Being - Satisfaction with Life

Satisfaction with life was assessed using the satisfaction with life scale[25]. The satisfaction with life scale contains 5 items measuring global cognitive judgments of satisfaction with one's life on a scale from 1 (strongly disagree) to 7 (strongly agree). Items were summed to calculate an individual's final score ranging from 0 to 35. A mean was calculated when satisfaction with life was assessed on more than one occasion. In total, data on satisfaction with life were available for 5344 individuals.

Subjective Well-Being - Happiness

Happiness was assessed using an adaptation of the subjective happiness scale[26]. The adapted subjective happiness scale contains 4 items measuring global subjective happiness on a scale from 1 (strongly disagree) to 7 (strongly agree). Items were summed to calculate an individual's final score, ranging from 0 to 28. A mean was calculated when subjective happiness was assessed on more than one occasion. In total, data on subjective happiness were available for 5350 individuals.

Depressive Symptoms

Depressive symptoms were assessed using the DSM-oriented depressive problem scale of the Adult Self Report[27]. This scale contains 14 items measuring depression symptoms on a scale from 0 to 2 (0= not true, 1= somewhat true, 2= very true or often true). The items were summed to create a sum score ranging from 0 to 28, a higher score representing higher levels of depressive symptoms. A mean was calculated when the depression problems were assessed on more than one occasion. In total, data on depressive symptoms were available for 8667 participants.

Loneliness

Loneliness was assessed using the short scale for assessing loneliness in large epidemiological studies[28,29]. This scale contains 3 items from the R-UCLA loneliness scale and asks participants to score how often they identify with the items on a scale from 1 to 3 (1= hardly ever, 2= some of the time, 3=often). The items were summed to obtain a sumscore with possible scores between 3 and 9, a higher score representing higher levels of loneliness. In total, data on loneliness were available for 8817 participants. A mean was calculated when loneliness was assessed on more than one occasion. We log-transformed the loneliness scores since they were highly positively skewed.

Personality

The Big Five personality traits were measured using the NEO-FFI[30,31]. This scale measures the Big Five personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism) with 60 items in total. Participants were asked to respond on a 5-point scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The 12 items per trait were summed to obtain one sumscore for each personality trait with possible scores between 12 and 60, a higher score representing higher levels of that particular personality trait. When personality data were available for more than one occasion, we calculated an individual's mean personality score per scale. In total, data on each personality scale were available for 8622 individuals.

Self-Rated Health

Self-rated health was assessed using a single item: "How, in general, is your health?"[32]. The item was rated on a 5-point scale, on which participants could respond with: "Bad", "Poor", "Fair", "Good" or "Excellent". A mean was calculated when Self-rated health was assessed on more than one occasion. In total, 8667 participants had data available for self-rated health.

Flourishing

Flourishing was assessed using the Flourishing Scale[33]. This scale contains 8 items measuring a person's self-perceived success in multiple life domains on a scale from 1 to 7, ranging from strong disagreement to strong agreement. The items were summed to create a sumscore ranging from 8 to 56, a higher score representing higher levels of positive flourishing. In total, data on flourishing were available for 2200 participants.

Genotyping, Quality Control, Imputation, and PCA

Genotyping was done on several genome-wide SNP micro-arrays[24]. Genotyped data were cross-platform imputed using the Genome of the Netherlands (GoNL)[34,35] as a reference set to infer the SNPs missing per platform in the combined data[36]. Alleles with reference set allele frequency differences of >10%, SNPs with MAF <.005, deviation from Hardy-Weinberg Equilibrium with $p<10^{-12}$, and a genotyping call rate <.95 were excluded for pre-imputation quality control. Samples that had a genotyping call rate <.90, inbreeding coefficient from PLINK (F) < -.075 or >.075[37], Affymetrix Contrast Quality Control metric <.40, Mendelian error rate >5 standard deviations from the mean, or gender or Identity-by-State status that did not agree with known relationship status and genotypic assessment were excluded. MaCH-Admix software[38] was used for phasing and imputation. SNPs that were significantly associated with genotyping platform ($p<10^{-5}$), that had an allele frequency difference of >10% with GoNL reference set, HWE $p<10^{-5}$, Mendelian error rate >5 SD from the mean over all markers, or an imputation quality R^2<.90 after imputation were excluded. In order to exclude individuals with a non-Dutch ancestry and to control for Dutch population stratification, we performed Principal Components Analysis (PCA) following procedures described by Abdellaoui et al. (2013). The remaining SNPs (N=1,224,793) were used to construct polygenic scores.

Phenotypic Correlations

Phenotypic correlations were calculated between all the traits using the gee package to correct for familial relatedness using in R statistical software[40]. The results were visualized using the corrplot package. The significance threshold for the phenotypic correlations was set at a Bonferonni corrected value of α =.005/55 = 0.00009, where 55 represents the number of correlations that were calculated in total.

Table I : Sample characteristics

Trait	Age *M*(*SD*)	*N* participants (% males)	Score *M*(*SD*)
Satisfaction with Life	40.94(15.83)	5344 (37.18%)	26.96(4.70)
Happiness	39.36(15.59)	5350 (37.14%)	22.48(4.17)
Neuroticism	42.09(15.94)	8622 (36.29%)	22.21(8.10)
Depressive Symptoms	38.68 (16.00)	8667 (36.45%)	3.58(3.19)
Loneliness	43.38(16.37)	8817 (36.43%)	3.82(1.03)
Openness to Experience	42.09(15.94)	8622 (36.29%)	29.65(6.58)
Conscientiousness	42.09(15.94)	8622 (36.29%)	37.96(6.28)
Extraversion	42.09(15.94)	8622 (36.29%)	34.27(6.73)
Agreeableness	42.09(15.94)	8622 (36.29%)	37.42(5.98)
Self-Rated Health	38.44(15.68)	8667 (39.26%)	4.07(.59)
Flourishing	40.16(14.96)	2200 (35.95%)	46.84(6.47)

Power Analysis

We used an online power-calculator based on code provided by Dudbridge (2013) to investigate whether the 3-WBS summary statistics[8] had sufficient power to predict the phenotypes that are considered to become part of the well-being spectrum. The power was computed as a function of the following discovery trait parameters: 1) the discovery sample size set based on the maximum sample size from the multivariate analyses (2,370,390) and 2) the discovery trait SNP heritability (h_{snp}) set at 0.02. Concerning the target trait parameters, we adjusted the parameters according to the different phenotypes mentioned above and set the significance threshold at a Bonferroni corrected value of $\alpha = .005/11 = 0.0005$, where 11 represents the number of phenotypes to be predicted with the polygenic scores. Table II shows an overview of the different input parameters and the results of the power analyses. The estimated SNP heritability for personality, self-rated health, loneliness, and depressive symptoms was based on results from previous studies[9,42–44]. The SNP heritability for the 3-WBS was estimated using LD score regression[45]. Since there has been no genome-wide association study for flourishing, we estimated the SNP heritability to be approximately as high as the SNP heritability for subjective well-being and meaning in life, which are estimated at ~.04[9] and ~.06[17], respectively. The power for all traits was very high, assuming a medium

to high genetic correlation, with the exception of flourishing, where (due to smaller sample and low SNP heritability) the power to detect effects was somewhat lower, around .60 (assuming a genetic correlation of ~.8).

Table II. *Power Calculation Parameters for the Polygenic Prediction*

Discovery Trait Parameters						
	N_{obs}	SNP heritability				
Well-Being Spectrum	2370390	0.021				
Target Trait Parameters						
	Input Sample Size	SNP heritability	Power if r_g=.2	Power if r_g=.4	Power if r_g=.6	Power if r_g=.8
Subjective Well-Being	5300	0.04	.07	.46	.90	.99
Neuroticism	8600	0.12	.56	.99	1	1
Depressive Symptoms	8600	0.05	.18	.70	.99	1
Loneliness	8800	0.16	.74	1	1	1
Openness to Experience	8600	0.11	.51	.99	1	1
Conscientiousness	8600	0.10	.45	.99	1	1
Extraversion	8600	0.18	.79	1	1	1
Agreeableness	8600	0.09	.4	.99	1	1
Self-Rated Health	8600	0.13	.61	.99	1	1
Flourishing	2200	0.04	.02	.15	.44	.77

Polygenic Prediction

The polygenic scores were created using LDpred[46]. LDpred takes into account linkage disequilibrium (LD) among SNPs in creating the polygenic risk scores. We calculated the mean causal effect size of each marker using the SNP effect sizes from the recent multivariate 3-WBS GWAMA, where SNP effects were reversed for depressive symptoms and neuroticism, ensuring that a higher score reflects higher levels of well-being[8]. The LD structure from the European populations in the 1000 Genomes reference set[47] was used to calculate polygenic scores in the target sample. In order to avoid an over-estimation of the association between the polygenic scores and phenotypes, summary statistics in the discovery set were re-computed, excluding NTR subjects. The polygenic scores were calculated with the expected fraction of causal genetic variants (the fraction of markers with non-zero effects) set at .10. Generalized Estimating Equation (GEE) modelling was used to test whether the 3-WBS polygenic scores significantly predict satisfaction with life, happiness, neuroticism, depressive symptoms, loneliness, openness to experience, conscientiousness, extraversion, agreeableness, self-rated health, and flourishing. An exchangeable conditional covariance

matrix was used to account for family relatedness and tests were based on robust (sandwich-corrected) standard errors[48]. Age, age^2, sex, and the first ten genomic principal components (PCs) (three ancestry-informative PCs and seven PCs accounting for genotyping batch effects) were included as covariates. To obtain 95% confidence intervals (CI) around the R^2's, we performed bootstrapping with 2000 repetitions. All analyses were performed in R[40].

Genetic Correlations

We used LD score regression[45] to compute the genetic correlations between the 3-WBS and the candidate traits for which GWAS summary statistics were available. This method distinguishes bias and inflation from a true polygenic signal by quantifying the contribution of each through examining the relationship between linkage disequilibrium and test statistics. For neuroticism, depressive symptoms, positive affect, and life satisfaction, we used the univariate summary statistics from the multivariate 3-WBS GWAMA[8]. For all personality measures except neuroticism, we used summary statistics from a subset of 23andme participants[42].

We obtained summary statistics for self-rated health and loneliness by running GWASs on data from UK Biobank (UK Biobank ID 20459 and 2020, respectively). Genome-wide association analyses were performed in PLINK[37] in a linear regression model of additive allelic effects. Standard pre-GWAS- quality control filters were applied, which included removing SNPs with minor allele frequency < 0.005 and/or with an INFO-score < 0.8 for imputed SNPs, and removing individuals with ambiguous sex and/or non-British ancestry. Furthermore, we randomly selected 1 individual from each closely related pair of relatives (i.e. parent offspring pairs, sibling pairs). The GWAS included 40 principal components, age, sex, and a chip dummy as covariates. The summary statistics from these GWASs were used as input for LD score regression analyses. The significance threshold for the genetic correlations was set at a Bonferonni corrected value of $\alpha = .005/55 = 0.00009$).

Results

Figure 1 (and Online Resource 1) shows the phenotypic correlation structure between the traits as measured in the NTR. The well-being phenotypes satisfaction with life and happiness were significantly associated with all traits except openness to experience. Neuroticism was associated with all traits except conscientiousness. All traits were significantly correlated with depressive symptoms. The 3-WBS traits were most significantly associated with each other, followed by the correlations between the 3-WBS phenotypes and loneliness (weakest *r*=-.38 and strongest *r*=.54), self-rated health (weakest *r*=-.24 and strongest *r*= .34), and flourishing (weakest *r*=-.29 and strongest *r*=.40).

Figure. 1 Phenotypic Correlations Between the Different Traits. SWL= Satisfaction with Life, HAP = Happiness, NEU= Neuroticism, DEP= Depressive Symptoms, LON= Loneliness, OPEN= Openness to Experience, CON= Conscientiousness, EXTR = Extraversion, AGREE= Agreeableness, SRH= Self-Rated Health, FLOUR= Flourishing. Upper triangle, phenotypic correlation displayed in numbers, where red coloured numbers are negative phenotypic correlations and blue coloured numbers are positive phenotypic correlations. Lower triangle is a visualisation of the strength of the phenotypic correlations.

Figure 2 (and Online Resource 2) show the results from the GEE analyses where the polygenic scores for the 3-WBS were used to predict the eleven outcome variables. As a proof of principle, we found that the traits used to create the polygenic scores (satisfaction with life, happiness, neuroticism, and depressive symptoms) were significantly associated (standardized *b*= between -.123 and .084) with the polygenic score. From the candidate traits to be added to

a well-being spectrum, four were significantly associated with the 3-WBS polygenic score. The strongest association was found for loneliness (standardized b=-.091, p=3.14 x 10^{-16}, R^2= 0.84%), followed by self-rated health (standardized b=.083, p=3.71 x 10^{-14}, R^2= 0.69%) and extraversion (standardized b=.069, p=6.63 x 10^{-9}, R^2= 0.47%). Conscientiousness, agreeableness and flourishing were not significantly associated with the 3-WBS polygenic score.

Fig. 2 The amount of variance explained by the polygenic risk score for each of the traits. SWL= Satisfaction with Life, HAP = Happiness, NEU= Neuroticism, DEP= Depressive Symptoms, LON= Loneliness, OPEN= Openness to Experience, CON= Conscientiousness, EXTR = Extraversion, AGREE= Agreeableness, SRH= Self-Rated Health, FLOUR= Flourishing

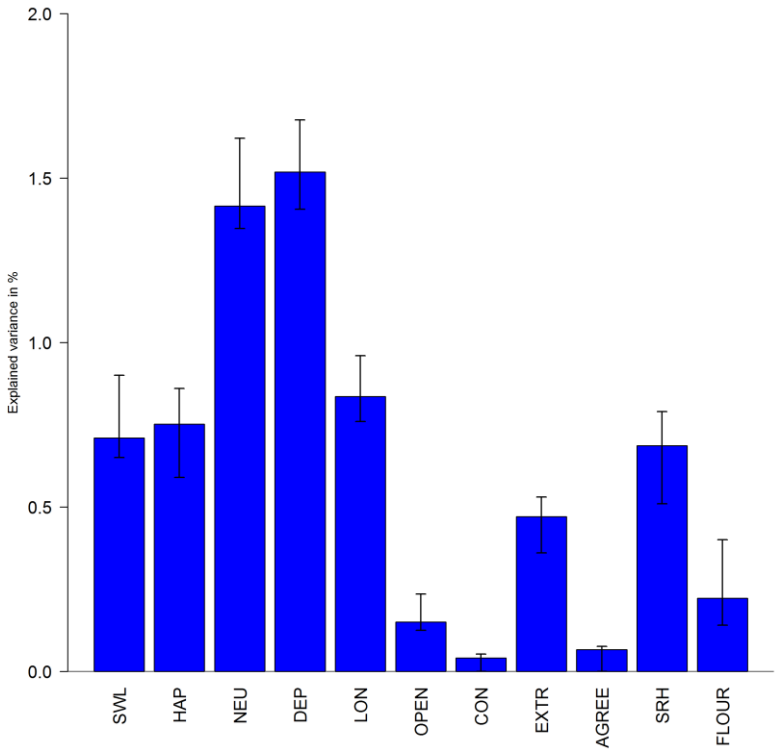
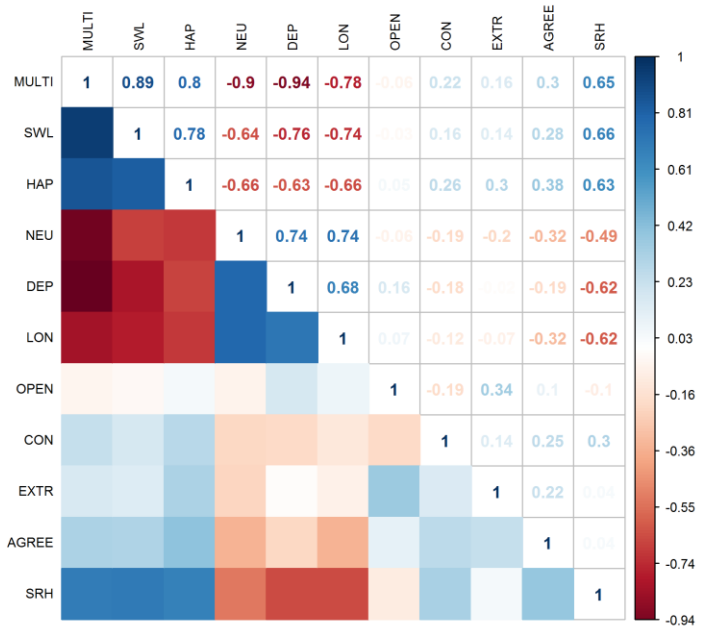


Figure 3 (and Online Resource 3) depict the genetic correlations obtained using LD score regression. As expected, the genetic correlations were strongest between the 3-WBS and the traits originally included in the spectrum, life satisfaction (r_g = .89), positive affect (r_g = .80), neuroticism (r_g = -.90), and depressive symptoms (r_g = -.94). Next, loneliness had the strongest genetic correlation with 3-WBS (r_g = .78), followed by self-rated health (r_g = .65), agreeableness (r_g = .30), conscientiousness (r_g = .22), and extraversion (r_g = .16). The only

trait that did not have a significant genetic association with 3-WBS was openness to experience (r_g = .06).

Fig. 3 Genetic Correlations Between the Different Traits. WB= Well-Being Spectrum, SWL= Satisfaction with Life, PA = Positive Affect, NEU= Neuroticism, DEP= Depressive Symptoms, LON= Loneliness, OPEN= Openness to Experience, CON= Conscientiousness, EXTR = Extraversion, AGREE= Agreeableness, SRH= Self-Rated Health. Upper triangle, genetic correlation displayed in numbers, where red coloured numbers are negative genetic correlations and blue coloured numbers are positive genetic correlations. Lower triangle is a visualisation of the strength of the genetic correlations.



Discussion

Well-being is a broad construct, with many traits contributing to its variation. In this study, we applied two types of genetic analyses to examine the genetic boundaries of a well-being spectrum. The traits we examined included the 3-WBS, as well as loneliness, openness to experience, conscientiousness, extraversion, agreeableness, self-rated health, and flourishing, conscientiousness, agreeableness, and openness to experience. First, we used publicly available GWAMA summary statistics to construct polygenic scores that reflect a genetic propensity for higher levels of well-being to predict several traits that have previously been associated with well-being. Second, we calculated genetic correlations between the 3-WBS and these traits.

The strongest associations with the polygenic score for the 3-WBS were found for the traits originally included in this spectrum. This shows that the scores are a good reflection of the proposed well-being spectrum when it is split up into its subdomains and supports the earlier findings of shared risk genes for these domains[9]. Moreover, these traits show high genetic correlations with the 3-WBS, as well as with each other, confirming previous findings that indicated high genetic correlations between life satisfaction, positive affect, neuroticism, and depressive symptoms[9].

Out of all candidate traits, loneliness showed the strongest phenotypic and genetic correlation with the well-being spectrum. As expected, lower well-being was found in people reporting higher levels of loneliness. The 3-WBS polygenic score predicted loneliness to a similar extent as it predicted subjective well-being measures. Even though the polygenic score predicted only a small amount of the variation in loneliness (0.84%), the genetic correlation between loneliness and well-being was in the same range as the that of the traits in the 3-WBS amongst themselves. Given these high phenotypic and genetic correlations, loneliness is a first good candidate to be added to the well-being spectrum.

Self-rated health constitutes a second good candidate. Self-rated health is a subjective measure of how individuals rate their current health status and has been established a good predictor of important objective health measures, such as mortality and the use of health services[49]. The 3-WBS polygenic score was found to predict self-rated health to a similar extent as subjective well-being. The genetic correlation between self-rated health and the 3-WBS was also relatively high (r_g= .65) confirming that people with a genetic predisposition for higher levels of well-being are more likely to rate themselves positively concerning their

health. For personality, we report a genetic association between the 3-WBS and extraversion and conscientiousness, but not for openness to experience or agreeableness. These results suggest that individuals with a genetic predisposition for higher levels of extraversion and conscientiousness also have a genetic predisposition to experience higher levels of well-being. These findings are in line with previous studies identifying extraversion and conscientiousness (in addition to neuroticism) as the strongest personality correlates of well-being[50,51]. Moreover, these results further support the findings by Weiss, Bates & Luciano (2008), where the genetic variance underlying subjective well-being was also responsible for individual differences in neuroticism, extraversion, and conscientiousness. The finding that openness to experience was not associated with well-being at a phenotypic and genetic level was not surprising and also found in previous research.

The genetic correlations revealed that only a small part of the genes that are important for extraversion and conscientiousness are also associated with well-being. Whereas the genetic correlation between agreeableness and well-being suggested they also share genetic factors, the polygenic score did not predict agreeableness. As shown in our power analyses, the power to predict agreeableness, given a genetic correlation of ~.30, is between .4 and .99. Therefore, it is likely that this seemingly contradictory finding is a result of the polygenic prediction for agreeableness having too little power to detect a polygenic association. Taken together, the evidence for a genetic correlation between well-being and multiple personality domains do not strongly support the inclusion of personality traits other than neuroticism in the well-being spectrum. A surprising finding was that the polygenic score did not significantly predict flourishing. Since the flourishing scale is a measure of PWB, and PWB is phenotypically highly associated with subjective well-being[52,53], we expected that, in line with the recent work of Baselmans and Bartels[17], part of this association could be explained by genetic factors. Two explanations are possible for our observations. The first explanation is that the relationship between 3-WBS and PWB as defined in this study is mainly a result of environmental factors. The second explanation is that, since our study had relatively low power to detect associations for flourishing, there is genetic overlap, but that these genetic effects remained unnoticed in this study. Unfortunately, we could not calculate the genetic correlation between the 3-WBS and flourishing due the constraint of the absence of a genome-wide association summary statistics for flourishing. However, future studies with larger sample sizes for PWB measures could elucidate which of these explanations is correct.

We note that the genetic correlations suggest large genetic overlap between the several traits, whereas the polygenic risk scores only explain a small part of the variance in each trait even with our large discovery sample. This discrepancy can be expected since the genotyped SNPs do not necessarily tag all causal variants, and not all SNPs were genotyped. Moreover, since measurement error accumulates across all the markers, sampling variation has a large influence on the predictive accuracy of the polygenic score[41]. We are therefore optimistic that, with increasing sample sizes and increased accuracy in the estimation of SNP effects, well-being polygenic scores will turn into clinically relevant tools for the prediction of outcomes such as loneliness or depression.

While these results provide us with important information on the genetic architecture of the well-being spectrum, the results should be interpreted with caution. As shown in Table II, the power of the polygenic prediction is dependent on sample size, especially when the genetic correlation between traits is low. Thus, better predictive accuracy and power could be achieved with larger sample sizes. Moreover, while including more traits in the well-being spectrum can lead to greater power for detecting genetic variants, the number of genetic variants influencing all traits will decline.

The results from the present study provide us with useful information on the determinants of individual differences in human well-being. Even though not all traits examined here can be included in the well-being spectrum from a genetic point of view, most of them are phenotypically and genetically related to well-being. It is important to know these determinants, since it could help us improve policy making and clinical interventions aimed at improving human well-being.

To conclude, in this study we found evidence for a shared genetic aetiology between several traits associated with well-being. The strongest relationships were found for loneliness and self-rated health. Our findings suggest that these two traits should be further investigated for potential inclusion in the well-being spectrum to increase our understanding of the causes and links between well-being and several mental/behavioural traits.

References

1. Koenen, K. C. *et al.* Common genetic liability to major depression and posttraumatic stress disorder in men. *J. Affect. Disord.* **105,** 109–115 (2008).
2. Bramon, E. & Sham, P. C. The common genetic liability between schizophrenia and bipolar disorder: a review. *Curr. Psychiatry Rep.* **3,** 332–7 (2001).
3. Peerbooms, O. L. J. *et al.* Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: Evidence for a common genetic vulnerability? *Brain. Behav. Immun.* **25,** 1530–1543 (2011).
4. Keyes, C. L. M. The mental health continuum: from languishing to flourishing in life. *J. Health Soc. Behav.* **43,** 207–22 (2002).
5. Chmiel, M., Brunner, M., Martin, R. & Schalke, D. Revisiting the Structure of Subjective Well-Being in Middle-Aged Adults. *Soc. Indic. Res.* **106,** 109–116 (2012).
6. Diener, E. & Chan, M. Y. Happy People Live Longer: Subjective Well-Being Contributes to Health and Longevity. *Appl. Psychol. Heal. Well-Being* **3,** 1–43 (2011).
7. Ryan, R. M. & Deci, E. L. On happiness and human potentials: a review of research on hedonic and eudaimonic well-being. *Annu. Rev. Psychol.* **52,** 141–166 (2001).
8. Baselmans, B. M. L. *et al.* Multivariate Genome-wide and integrated transcriptome and epigenome-wide analyses of the Well-being spectrum. *bioRxiv* **115915,** 1–27 (2017).
9. Okbay, A. *et al.* Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat. Genet.* **48,** 624–633 (2016).
10. Soto, C. J. Is Happiness Good for Your Personality? Concurrent and Prospective Relations of the Big Five With Subjective Well-Being. *J. Pers.* **83,** 45–55 (2015).
11. DeNeve, K. M. & Cooper, H. The happy personality: a meta-analysis of 137 personality traits and subjective well-being. *Psychol. Bull.* **124,** 197–229 (1998).
12. Cacioppo, J. T., Hawkley, L. C. & Thisted, R. A. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychol. Aging* **25,** 453–463 (2010).
13. Ben-Zur, H. Loneliness, Optimism, and Well-Being Among Married, Divorced, and Widowed Individuals. *J. Psychol.* **146,** 23–36 (2012).
14. Larson, R. Thirty years of research on the subjective well-being of older americans. *J. Gerontol.* **33,** 109–125 (1978).
15. Okun, M. A. & George, L. K. Physician- and self-ratings of health, neuroticism and subjective well-being among men and women. *Pers. Individ. Dif.* **5,** 533–539 (1984).
16. Kashdan, T. B., Biswas-Diener, R. & King, L. A. Reconsidering happiness: the costs of distinguishing between hedonics and eudaimonia. *J. Posit. Psychol.* **3,** 219–233 (2008).
17. Baselmans, B. M. L. & Bartels, M. A genetic perspective on the relationship between eudaimonic -and hedonic well-being. *bioRxiv* (2018).
18. Abdellaoui, A. *et al.* Predicting loneliness with polygenic scores of social, psychological and psychiatric traits. *Genes, Brain Behav.* (2018). doi:10.1111/gbb.12472
19. Roysamb, E., Tambs, K., Reichborn-Kjennerud, T., Neale, M. C. & Harris, J. R. Happiness and health: Environmental and genetic contributions to the relationship between subjective well-being, perceived health, and somatic illness. *J. Pers. Soc. Psychol.* **85,** 1136–1146 (2003).
20. Keyes, C. L. M., Myers, J. M. & Kendler, K. S. The structure of the genetic and environmental influences on mental well-being. *Am. J. Public Health* **100,** 2379–2384 (2010).

21. Weiss, A., Bates, T. C. & Luciano, M. Happiness is a personal(ity) thing: The genetics of personality and well-being in a representative sample. *Psychol. Sci.* **19,** 205–10 (2008).
22. Weiss, A. *et al.* Personality Polygenes, Positive Affect, and Life Satisfaction. *Twin Res. Hum. Genet.* **19,** 407–417 (2016).
23. Boomsma, D. I. *et al.* Netherlands Twin Register: from twins to twin families. *Twin Res. Hum. Genet.* **9,** 849–857 (2006).
24. Willemsen, G. *et al.* The Adult Netherlands Twin Register: twenty-five years of survey and biological data collection. *Twin Res. Hum. Genet.* **16,** 271–81 (2013).
25. The Satisfaction With Life Scale. Available at: http://internal.psychology.illinois.edu/~ediener/Documents/Diener-Emmons-Larsen-Griffin_1985.pdf. (Accessed: 20th August 2015)
26. Lyubomirsky, S. & Lepper, H. S. A measure of subjective happiness: Preliminary reliability and construct validation. *Soc. Indic. Res.* **46,** 137–155 (1999).
27. Achenbach, T. M. & Rescorla, L. *Manual for the ASEBA adult forms & profiles*. (Burlington, VT: University of Vermont, 2003).
28. Hughes, M. E., Waite, L. J., Hawkley, L. C. & Cacioppo, J. T. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. *Res. Aging* **26,** 655–672 (2004).
29. Distel, M. A. *et al.* Familial Resemblance for Loneliness. *Behav. Genet.* **40,** 480–494 (2010).
30. Costa, P. T. & McCrae, R. R. *Revised NEO personality inventory (NEO PI-R) and NEO five-factor inventory (NEO-FFI) professional manual*. (Psychological Assessment Resources Inc., Odessa, 1992).
31. Franić, S., Borsboom, D., Dolan, C. V. & Boomsma, D. I. The Big Five Personality Traits: Psychological Entities or Statistical Constructs? *Behav. Genet.* **44,** 591–604 (2014).
32. Eriksson, I., Undén, A. L. & Elofsson, S. Self-rated health. Comparisons between three different measures. Results from a population study. *Int. J. Epidemiol.* **30,** 326–33 (2001).
33. Diener, E. *et al.* New Well-being Measures: Short Scales to Assess Flourishing and Positive and Negative Feelings. *Soc. Indic. Res.* **97,** 143–156 (2010).
34. Boomsma, D. I. *et al.* The Genome of the Netherlands: design, and project goals. *Eur. J. Hum. Genet.* **22,** 221–227 (2014).
35. The Genome of the Netherlands Consortium. Whole-genome sequence variation, population structure and demographic history of the Dutch population. *Nat. Genet.* **46,** 818–825 (2014).
36. Fedko, I. O. *et al.* Estimation of Genetic Relationships Between Individuals Across Cohorts and Platforms: Application to Childhood Height. *Behav. Genet.* **45,** 514–528 (2015).
37. Purcell, S. *et al.* PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *Am. J. Hum. Genet.* **81,** 559–575 (2007).
38. Liu, E. Y., Li, M., Wang, W. & Li, Y. MaCH-Admix: Genotype Imputation for Admixed Populations. *Genet. Epidemiol.* **37,** 25–37 (2013).
39. Abdellaoui, A. *et al.* Population structure, migration, and diversifying selection in the Netherlands. *Eur. J. Hum. Genet.* **21,** 1277–85 (2013).
40. R Core Team. R: A language and environment for statistical computing. (2013).

41. Dudbridge, F. Power and Predictive Accuracy of Polygenic Risk Scores. *PLoS Genet.* **9,** e1003348 (2013).
42. Lo, M.-T. *et al.* Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nat. Genet.* **49,** 152–156 (2017).
43. Gao, J. *et al.* Genome-Wide Association Study of Loneliness Demonstrates a Role for Common Variation. *Neuropsychopharmacology* **42,** 811–821 (2017).
44. Harris, S. E. *et al.* Molecular genetic contributions to self-rated health. *Int. J. Epidemiol.* **58,** dyw219 (2016).
45. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47,** 291–5 (2015).
46. Vilhjálmsson, B. J. *et al.* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am. J. Hum. Genet.* **97,** 576–592 (2015).
47. Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526,** 68–74 (2015).
48. Minica, C. C., Boomsma, D. I., Vink, J. M. & Dolan, C. V. MZ twin pairs or MZ singletons in population family-based GWAS? More power in pairs. *Mol. Psychiatry* **19,** 1154–1155 (2014).
49. Silventoinen, K., Posthuma, D., Lahelma, E., Rose, R. J. & Kaprio, J. Genetic and Environmental Factors Affecting Self-Rated Health from Age 16-25: A Longitudinal Study of Finnish Twins. *Behav. Genet.* **37,** 326–333 (2007).
50. Hayes, N. & Joseph, S. Big 5 correlates of three measures of subjective well-being. *Pers. Individ. Dif.* **34,** 723–727 (2003).
51. Grant, S., Langan-Fox, J. & Anglim, J. The Big Five Traits as Predictors of Subjective and Psychological Well-Being. *Psychol. Rep.* **105,** 205–231 (2009).
52. Nave, C. S., Sherman, R. A. & Funder, D. C. Beyond self-report in the study of hedonic and eudaimonic well-being: Correlations with acquaintance reports, clinician judgments and directly observed social behavior. *J. Res. Pers.* **42,** 643–659 (2008).
53. Vanhoutte, B. & Nazroo, J. Cognitive, Affective and Eudemonic Well-Being in Later Life: Measurement Equivalence over Gender and Life Stage. *Sociol. Res. ONLINE* **19,** (2014).

Supplementary Information

Supplementary Table 1

Phenotypic Correlations Between the Traits (NTR Data).

	SWL	HAP	NEU	DEP	LON	OPEN	CON	EXTR	AGREE	SRH	FLOUR
SWL	1	-	-	-	-	-	-	-	-	-	-
HAP	.65*	1	-	-	-	-	-	-	-	-	-
NEU	-.48*	-.47*	1	-	-	-	-	-	-	-	-
DEP	-.48*	-.45*	.61*	1	-	-	-	-	-	-	-
LON	-.45*	-.38*	.54*	.53*	1	-	-	-	-	-	-
OPEN	-.01	<.01	.32*	.08*	.12*	1	-	-	-	-	-
CON	.23*	.20*	.01	-.29*	-.15*	.34*	1	-	-	-	-
EXTR	.28*	.33*	-.05*	-.33*	-.21*	.38*	.58*	1	-	-	-
AGREE	.11*	.11*	.20*	-.09*	-.06*	.44*	.54*	.49*	1	-	-
SRH	.34*	.24*	-.31*	-.34*	-.21*	.02	.12*	.20*	.04	1	-
FLOUR	.40*	.32*	-.29*	-.30*	-.26*	.06	.26*	.30*	.17*	.23*	1

Note. NEU= Neuroticism, DEP= Depressive Symptoms, SWL= Satisfaction with Life, HAP = Happiness, LON= Loneliness, SRH= Self-Rated Health, EXTR = Extraversion, FLOUR= Flourishing, CON= Conscientiousness, AGREE= Agreeableness, OPEN= Openness to Experience.

*p-value significant at α=.00009 (0.005/55).

Supplementary Table 2

Outcomes GEE analyses

Outcome Variable	**Standardized *b*(*se*)**	***P*-value**	R^2
Satisfaction with Life	.084(.015)	2.15×10^{-8}*	0.71
Happiness	.087(.015)	7.81×10^{-9}*	0.75
Neuroticism	-.119(.012)	$5.3x\ 10^{-23}$*	1.42
Depressive Symptoms	-.123(.012)	$7.57x\ 10^{-25}$*	1.52
Loneliness	-.091(.011)	3.14×10^{-16}*	0.84
Openness to Experience	-.039(.012)	0.002	0.15
Conscientiousness	.020(.012)	0.092	0.04
Extraversion	.069(.012)	6.63×10^{-9}*	0.47
Agreeableness	.026(.012)	0.027	0.07
Self-Rated Health	.083(.011)	3.71×10^{-14}*	0.69
Flourishing	.047(.047)	0.027	0.22

*p-value significant at α=.0005.

Supplementary Table 3

Genetic Correlations (SE) Between the Different Traits (Data From Several GWAS).

	MULTI	SWL	PA	NEU	DEP	LON	OPEN	CON	EXTR	AGREE	SRH
MULTI	1	-	-	-	-	-	-	-	-	-	-
SWL	.889(.084)*	1	-	-	-	-	-	-	-	-	-
PA	.798(.014)*	.777(.051)*	1	-	-	-	-	-	-	-	-
NEU	-.902(.006)*	-.645(.057)*	-.660(.018)*	1	-	-	-	-	-	-	-
DEP	-.937(.004)*	-.759(.085)*	-.631(.023)*	.738(.015)*	1	-	-	-	-	-	-
LON	-.781(.019)*	-.735(.068)*	-.658(.026)*	.740(.017)*	.678(.022)*	1	-	-	-	-	-
OPEN	-.056(.046)	-.029(.065)	.046(.043)	-.062(.048)	.162(.042)	.069(.051)	1	-	-	-	-
CON	.218(.042)*	.164(.068)	.258(.045)	-.194(.038)*	-.183(.043)*	-.117(.048)	-.187(.064)	1	-	-	-
EXTR	.155(.037)*	.137(.055)	.296(.034)*	-.204(.037)*	-.018(.036)	-.074(.038)	.341(.045)*	.145(.053)	1	-	-
AGREE	.299(.045)*	.284(.072)*	.375(.046)*	-.322(.047)*	-.192(.042)*	-.320(.055)*	.095(.073)	.252(.065)	.221(.052)	1	-
SRH	.652(.037)*	.663(.076)*	.629(.034)*	-.492(.046)*	-.617(.038)*	-.616(.044)*	-.098(.056)	.305(.054)*	.039(.047)	.036(.063)	1

Note. WB=Well-Being Spectrum, NEU= Neuroticism, DEP= Depressive Symptoms, SWL= Satisfaction with Life, PA= Positive Affect, LON= Loneliness, SRH= Self-Rated Health, EXTR= Extraversion, CON= Conscientiousness, AGREE= Agreeableness, OPEN= Openness to Experience.
*p-value significant at α= .00009 (0.005/55)